A Statistical Deformation Model (SDM) based Regularizer for Non-rigid Image Registration: Application to registration of multimodal prostate MRI and histology.

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ABSTRACT

Free form deformation (FFD) is a popular algorithm for non-linear image registration because of its ability to accurately recover deformations. However, due to the unconstrained nature of elastic registration, FFD may introduce unrealistic deformations, especially when differences between template and target image are large, thereby necessitating a regularizer to constrain the registration to a physically meaningful transformation. Prior knowledge in the form of a Statistical Deformation Model (SDM) in a registration scheme has been shown to function as an effective regularizer. With a similar underlying premise, in this paper, we present a novel regularizer for FFD that leverages knowledge of known, valid deformations to train a statistical deformation model (SDM). At each iteration of the FFD registration, the SDM is utilized to calculate the likelihood of a given deformation occurring and appropriately influence the similarity metric to limit the registration to only realistic deformations. We quantitatively evaluate robustness of the SDM regularizer in the framework of FFD through a set of synthetic experiments using brain images with a range of induced deformations and 3 types of multiplicative noise - Gaussian, salt and pepper and speckle. We demonstrate that FFD with the inclusion of the SDM regularizer yields up to a 19% increase in normalized cross correlation (NCC) and a 16% decrease in root mean squared (RMS) error and mean absolute distance (MAD). Registration performance was also evaluated qualitatively and quantitatively in spatially aligning ex vivo pseudo whole mount histology (WMH) sections and in vivo prostate MRI in order to map the spatial extent of prostate cancer (CaP) onto corresponding radiologic imaging. Across all evaluation measures (MAD, RMS, and DICE), regularized FFD performed significantly better compared to unregularized FFD.

Keywords: registration, deformation, prostate cancer, MRI, SDM, regularizer, free form deformation, radiology, pathology, digital pathology

1. BACKGROUND AND MOTIVATION

In recent years, magnetic resonance (MR) imaging (MRI) has emerged as a powerful modality for the staging of prostate cancer (CaP), with a range of studies illustrating that 3 Tesla (T) endorectal in vivo T2-weighted (T2-w) imaging provides higher contrast and resolution compared to ultrasound (US). Different MRI acquisition protocols (e.g. T2-w and diffusion weighted imaging (DWI)) allow for the analysis of key metabolic, functional, vascular, and structural characteristics of tissues under consideration. Compared to the use of a single MR imaging protocol, it has been demonstrated that the use of multiprotocol MRI significantly improves the specificity and sensitivity for CaP detection. Current clinical diagnostic protocol involves no image-based detection of CaP, therefore the ability to utilize in vivo multiprotocol images could potentially obviate the need for invasive screening of CaP and pave the way for noninvasive image-based screening, targeted biopsies and conformal radiation therapy.

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Figure 1: Shown are (a) an endorectal T2-w MRI with segmentation of the prostate capsule in blue and (b) a magnified view of (a) highlighting the shape of the prostate. The shape dissimilarity of the prostate on the corresponding (c) hematoxylin and eosin stained tissue section with ground truth for CaP extent accentuates the need for registration of \textit{ex vivo} histopathology and pre-operative \textit{in vivo} MRI.

To accurately distinguish cancerous from non-cancerous regions \textit{in vivo} via prostate MRI, the appearance of CaP needs to be quantitatively modeled using a set of training images on which disease extent has been delineated. The definition of such image signatures would not only have clear implications for a computer-assisted disease (CAD) detection system,\textsuperscript{3} but also spatial disease atlases which could serve as educational and training tools for medical students, radiology residents, and fellows. Since it is generally difficult even for an expert radiologist to annotate the cancerous regions directly on the pre-operative \textit{in vivo} MRI images, the delineation of disease extent on histopathology through microscopic analysis still remains the “gold standard”.\textsuperscript{4} For men undergoing radical prostatectomy due to biopsy confirmed CaP, pre-operative MRI images of the prostate gland could be aligned with the \textit{ex vivo} post-operative histological images. This allows for mapping the ground truth for spatial extent of CaP from histology to MRI.\textsuperscript{5,6}

The spatial correlation of diseased regions on histology and MRI may be performed by either (a) manually identifying and labeling corresponding structures on each modality\textsuperscript{7} or (b) using a semiautomated or fully automated image registration procedure.\textsuperscript{5} However, previous studies have demonstrated that manual labeling of cancer is prone to errors and subject to observer bias.\textsuperscript{5} Moreover, we have illustrated that with an accurate registration procedure to spatially align \textit{ex vivo} histopathology with \textit{in vivo} MRI, CaP extent on MRI can be established with greater accuracy, efficiency, and consistency compared to manual labeling.\textsuperscript{5} Registration algorithms are commonly categorized as either rigid, affine or non-rigid.\textsuperscript{8} Whereas rigid transformations are only composed of rotations and translations, affine transformations permit scaling and shearing of images as well. In contrast, non-rigid techniques introduce more flexibility in the process by increasing the number of degrees of freedom and allowing for all voxels to transform freely. Regardless of the classification, all registration tools are governed by a cost function that serves to maximize or minimize a similarity measure as images are brought into alignment. Until the best value of the cost function (i.e. a global maximum or minimum) is found, this alignment is adjusted iteratively.\textsuperscript{9} Figure 1 illustrates the need for an image registration algorithm for aligning the \textit{ex vivo} histopathology with the pre-operative MRI, given the significant shape differences.

The registration of \textit{ex vivo} radical prostatectomy histological sections with corresponding pre-operative \textit{in vivo} MRI sections is problematic on account of several reasons: (a) vast inherent difference in the appearance of tissue and anatomical structures, (b) considerable deformation as a result of the endorectal coil and structures surrounding the prostate as well as uneven tissue fixation, gland slicing, and sectioning, and (c) tissue loss due to acquisition of histology slices in quadrants. Because \textit{ex vivo} histological sections are obtained as quadrants, they must be digitally reconstituted together to form a pseudo whole mount histology (WMH) section. Such difficulties cannot be overcome with simplistic non-rigid approaches purely driven by intensity values evaluating divergent information on the two modalities. While pixel intensities on histology simply measure tissue stain uptake (in this case, hematoxylin and eosin), those on T2-w MRI represent water content. Therefore, a multi-modal image registration method relying solely on image intensities may not be able to address the significant
The free form deformation (FFD) algorithm\textsuperscript{10} is a popular non-rigid registration scheme. However, this fully automated approach proposed by Rueckert et al. fails in scenarios of multi-modal images with highly different appearance (e.g. histology and MRI) and artifacts such as noise.\textsuperscript{11} Additionally, FFD does not explicitly constrain the types of permissible deformations, as each pixel is truly able to deform freely, and as such can yield unrealistic deformations. In this article, we present a novel additive component to FFD that addresses registration problems stemming from noisy and highly heterogeneous data sets.

The rest of the paper is organized as follows. In section 2, previous work performed to use a statistical deformation model (SDM) with a registration scheme is detailed. Additionally, past attempts to register histology and MRI images of the prostate are also described. In section 3, we highlight the novel contributions of this work. In section 4, the construction of a statistical deformation model and incorporation in FFD are explained. In section 5, we provide an overview of the synthetic and clinical data sets, the experimental design and methods for registration evaluation. Section 6 presents the results from the registration tasks for both the synthetic and real cases. Concluding remarks and future direction are given in section 7.

2. PREVIOUS WORK

A regularizer is often exploited in image registration to overcome the limitations of FFD as described above and exclude unreasonable deformations.\textsuperscript{8} Given a range of possible transformations to optimize the similarity between two images, the regularizer eliminates those that do not preserve the physical meaning of the image and alternatively, encourages a robust and meaningful solution to the registration problem. At a high level, while some regularizers take the form of an additive term to the cost function, such as adding a very high term to the cost function in cases of unsmooth deformations,\textsuperscript{8} others take the form of intelligently constraining or smoothing the allowed deformations prior to calculation of the cost function. An example of the latter is particularly apparent in Thirion’s Demons algorithm,\textsuperscript{12} which computes a force vector for each pixel using the derivative of the similarity measure and then convolves the result with a Gaussian kernel.\textsuperscript{8}

Prior domain knowledge in the form of a statistical deformation model (SDM) too has been evaluated as a regularizer. The concept of utilizing a SDM for image registration stems from the notion of active shape models (ASM)\textsuperscript{13} in image segmentation. While ASMs are statistical models of shapes that are deformed to fit an object in a given image, SDMs are statistical models of deformation fields that actuate alignment of images in registration. To build an accurate SDM, an initial training set of typical, realistic deformations between the multimodal images to be aligned is required, analogous to the need for an initial set of landmarks to construct an ASM. By determining the mean and variance of the training data via principal component analysis (PCA), it is then possible to determine the standard score of a new occurrence of a deformation field based on the model. This can then be used in various ways to drive the registration towards a specific solution. It is important to note that while SDMs incorporate prior knowledge in the form of learning reasonable deformation fields, and can therefore be considered supervised, smoothness regularizers are inherently unsupervised.

Several groups in the past have identified that addition of SDM within a registration provides more accurate and appropriate results. Rueckert et al. initially proposed the statistical deformation model (SDM) as a form of prior knowledge in image registration to drive the anatomical alignment of certain regions in medical images.\textsuperscript{14} Albrecht et al. presented a probabilistic framework for non-rigid image registration that exploits a SDM to restrain the transformation. However, it is difficult to assess the performance of the scheme due to a single image similarity metric (sum of squared distances, SSD) being used. The authors did not report any quantitative results illustrating the effectiveness of the regularizer.\textsuperscript{15} Kim et al. further developed a PCA-based deformation model to expedite the non-rigid registration process by transforming the fixed image such that it bears greater resemblance to the moving image.\textsuperscript{16} Lastly, Xue et al. constructs a statistical model of deformation to use as a regularizer for 3D registration. Here, the presented regularizer functions properly even when only a limited number of training sets is available.\textsuperscript{17}

To the best of our knowledge, no methodologies based off a SDM regularizer have been used for a multimodal data set such as histology and MRI. However, some groups,\textsuperscript{18–21} including ours,\textsuperscript{5,22} have attempted to address this challenge in different ways; these studies have primarily utilized a thin plate spline (TPS) to model the elastic 2D
deformations of histology to ex vivo MRI of prostate specimens using control points. Additionally, often, “block face” photographs of thick tissue sections of prostate taken prior to microtome slicing and preparation were used to facilitate correction of nonlinear tissue deformations and in the creation of a histology volume. Park et al., for instance, used these photographs to overcome nonlinear deformations on histology and identify a one-to-one relationship between histology sections and slices in the MRI volume. But, such photographs are not generally acquired as part of routine clinical practice. Zhan et al. also performed registration of ex vivo MRI and histology sections using pairs of automatically detected control points in each modality. However, the automated identification of a large number of landmark pairs across ex vivo WMH and in vivo MRI (of lower image resolution and quality compared to ex vivo MRI) continues to be a major challenge.

More recently, the registration of in vivo radiologic images with WMH have been addressed. In a rat brain study, Meyer et al. exploited available block face photographs to generate a histology volume for 3D registration. This approach also utilized an intermediate ex vivo MRI series, to which WMH was aligned using a manual TPS-based approach, followed by mutual information driven refinement of the registration. Then, ex vivo MRI was registered to in vivo MRI, thus indirectly aligning the in vivo MRI and histology slices of the rat brains. Park et al. further extended this approach to the human prostate, again using block face photographs and ex vivo MRI as an intermediate. While the works of Park and Meyer successfully address the need to rely on approximate slice correspondences, neither block face photographs nor ex vivo MRI of prostate specimens are usually available in the course of the clinical workflow. This might also explain why only two patient studies were employed in [19] and one rat brain slide in [20]. Our group has attempted to register in vivo MRI and ex vivo histology using multiattribute combined mutual information (MACMI), which leverages all multiprotocol image data in conjunction with a multivariate formulation of mutual information to elastically register the two modalities. We have also explored spatially weighted mutual information (SWMI) to obviate the need for pre-segmentation of the prostate capsule on MRI and allow for fast, automatic registration to map CaP extent from WMH onto pre-operative MRI.

3. NOVEL CONTRIBUTIONS

In this work, we tackle the registration of ex vivo histopathology images of the prostate with pre-operative in vivo MRI by using a robust regularizer for FFD that exploits knowledge within a SDM to (1) ensure physically meaningful transformations, and (2) help overcome various types of artifacts such as noise in images. The SDM regularizer intelligently controls the registration by assigning a likelihood value for all proposed deformations within each iteration. The likelihood values are calculated from a SDM trained from a series of known deformations. Subsequently, the calculated likelihood value is scaled by a weighting parameter and added to the similarity metric to function as a penalty term. This serves to penalize deformations which are dissimilar from the trained deformations. We highlight the significance of this SDM regularizer by focusing not only on the registration of ex vivo WMH and in vivo MRI images of the prostate gland, but also on recovering synthetic deformations on BrainWeb data.

Our scheme for registration of in vivo MRI and ex vivo WMH is distinct from previous approaches in that (1) information from a SDM is leveraged to drive the process of automated non-rigid registration with histology; (2) no additional, intermediate ex vivo radiology or gross histology images need to be obtained in addition to the clinically acquired in vivo MRI series; and (3) no point correspondences are required to be identified manually or automatically. Furthermore, as with SWMI, our scheme does not require explicit segmentation of the prostate on MRI prior to registration with WMH. The novel aspects of the work presented in this paper are:

- a novel SDM regularizer that is not limited to SSD and compatible with MI, NCC and various other popular similarity measures, allowing for a wide range of applications.
- a novel method that uses the SDM regularizer to allow the registration to progress smoothly despite the presence of any artifacts that may be present in the image, as often found in medical imagery.
- a novel multimodality image registration routine that combines FFD with the SDM regularizer to downplay the influence of intensity-based information and register and map disease extent from ex vivo histology to in vivo MRI of the prostate.
<table>
<thead>
<tr>
<th>Symbol</th>
<th>Description</th>
<th>Symbol</th>
<th>Description</th>
</tr>
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<tbody>
<tr>
<td>$I^T$</td>
<td>2D Template image scene $I^T = (C^T, f)$</td>
<td>$T_{\text{gap}}$</td>
<td>Known, applied transformation</td>
</tr>
<tr>
<td>$I^M$</td>
<td>2D Moving image scene $I^M = (C^M, f)$</td>
<td>$T^{\text{MT}}$</td>
<td>Mean deformation field of training set</td>
</tr>
<tr>
<td>$C$</td>
<td>Coordinate grid of pixels in 2D image</td>
<td>$\beta$</td>
<td>Number of eigenvectors capturing 98% variance in training set</td>
</tr>
<tr>
<td>$g$</td>
<td>Single pixel in $C^T$</td>
<td>$\Psi$</td>
<td>Matrix of $\beta$ eigenvectors</td>
</tr>
<tr>
<td>$c$</td>
<td>Single pixel in $C^M$</td>
<td>$\lambda$</td>
<td>Eigenvalues corresponding to the set of eigenvectors in $\Psi$</td>
</tr>
<tr>
<td>$f(\cdot)$</td>
<td>Intensity at $c$ or $g$; $f(\cdot) \in \mathbb{R}$</td>
<td>$T^N$</td>
<td>New occurrence of a transformation</td>
</tr>
<tr>
<td>$T^{\text{MT}}$</td>
<td>Regularized transformation mapping $c \in C^M$ to new location $g \in C^T$</td>
<td>$T^{N'}$</td>
<td>Low dimensional projection of $T^N$</td>
</tr>
<tr>
<td>$T^{\text{MT}'}$</td>
<td>Unregularized transformation mapping $c \in C^M$ to new location $g \in C^T$</td>
<td>$T^{N''}_i$</td>
<td>$z$-score for principal component $i$ of $T^{N''}$</td>
</tr>
</tbody>
</table>

Table 1: Table of commonly used notation.

4. METHODOLOGY

4.1 Notation

We define $I$ as a 2D image scene by the notation $I = (C, f)$, where $C$ is a coordinate grid, called the scene domain, and $f$ is a function that assigns to every pixel $c \in C$ an intensity value $f(c)$. A list of notations and symbols commonly used in the rest of the paper are provided in Table I.

4.2 Regularized Registration Framework

Given a template image $I^T$ and moving image $I^M$, the image registration problem determines the mapping $T^{\text{MT}}: C^M \mapsto C^T$ and is expressed in the following manner:

$$T^{\text{MT}} = \arg \max_T S[I^T, T[I^M]] + \alpha \cdot R[T],$$

(1)

where the transformed moving image is defined as $T[I^M] = (C^T, f^M)$ so that every $c \in C^M$ is mapped to a new spatial location $g \in C^T$. $S$ is a similarity metric that quantifies the degree of spatial correspondence between $I^T$ and $T[I^M]$. Most common choices for similarity metrics are mutual information (MI), sum of squared distances (SSD) and normalized cross correlation (NCC). In the synthetic and clinical experiments detailed in the following sections, SSD and MI, respectively, drive the registrations. $R$ represents a regularizer that functions to limit the transformation $T$ if it is not reasonable. $\alpha$ is a constant used to scale the regularization term.

4.3 Training the SDM Regularizer

Assuming we have $n$ known transformations, $T^{\text{MT}}_i \in \{1, ..., n\}$, the first step is the calculation of the mean deformation field $T^{\text{MT}}$. An eigen-analysis is then performed on the training set, resulting in $\Psi \in \mathbb{R}[T^{\text{MT}}| \times \beta$, a matrix comprising the top $\beta$ eigenvectors with corresponding eigenvalues $\lambda = \{\lambda_1, ..., \lambda_\beta\}$. $\beta$ is chosen such that 98% of the variance in the training data is captured. Mathematically, $\beta$ is the largest number that satisfies the following expression:

$$\sum_{i=1}^{\beta} \lambda_i \leq 0.98 \cdot \sum_{i=1}^{T^{\text{MT}}|} \lambda_i,$$

(2)

where $|T^{\text{MT}}|$ is the cardinality of $T^{\text{MT}}$. 
Figure 2: Shown are examples of (a) the mean deformation field $T^{MT}$, (b) the first standard deviation $T^{N''}_1 = 1$ and (c) the tenth standard deviation $T^{N''}_{10} = 10$. Deformation fields diverging significantly from $T^{MT}$, as in (c), are constrained due to an assigned low likelihood value.

4.4 Using the SDM to Regularize FFD

Now, a given new transformation $T^N$ can be modeled using the constructed SDM by a low dimensional projection $T^{N'}$:

$$T^N = T^{MT} + \Psi \cdot T^{N'}.$$  \hspace{1cm} (3)

The log likelihood value of $T^N$ can be calculated using a form of the multivariate normal distribution equation:

$$R[T^N] = \log \left( \prod_{i=1}^{\beta} \frac{1}{\sqrt{2\pi\lambda_i}} \exp \left( -\frac{(T^N_i)^2}{2\lambda_i} \right) \right) = \sum_{i=1}^{\beta} \left( -\frac{1}{2} \cdot \log (2\pi\lambda_i) - \frac{(T^N_i)^2}{2\lambda_i} \right).$$  \hspace{1cm} (4)

Because $\lambda_i$ is predetermined and does not change at each iteration, Equation (4) can be reduced sequentially in the following manner:

$$R[T^N] = \sum_{i=1}^{\beta} \left( -\frac{1}{2} \cdot \log (2\pi\lambda_i) - \frac{(T^N_i)^2}{2\lambda_i} \right) - \sum_{i=1}^{\beta} \frac{(T^{N''}_i)^2}{2\lambda_i}.$$  \hspace{1cm} (5)

$$R[T^N] = c_1 + c_2 \sum_{i=1}^{\beta} \frac{(T^{N''}_i)^2}{2\lambda_i} = c_1 + c_2 \sum_{i=1}^{\beta} (T^{N''}_i)^2.$$  \hspace{1cm} (6)

where $T^{N''}_i$ represents the z-score for principal component $i$ of a new transformation $T^N$ and $c_1$ and $c_2$ are constants. For example, $T^{N''}_3 = 2$ represents a deformation field in which the third component is two standard deviations from the mean deformation field in the SDM. Figure 2 shows several deformation fields from a trained SDM with different numbers of standard deviations.

All the above calculations are performed at each iteration of FFD immediately following the generation of the transformation. The calculated log likelihood value is adjusted using $\alpha$ so that it is on the same order of magnitude as the similarity measure. The final value is then applied to the overall function, as described in Equation (1), to either limit, in the case of a low value, or allow, in the case of a high value, the transformation.
5. EXPERIMENTAL DESIGN

5.1 Synthetic brain MRI

5.1.1 Data Description
We consider a synthetic registration task using a data set $S$ consisting of 100 2D T1-w MRI slices, denoted $T_1$, from the BrainWeb simulated brain database. In a randomized fashion, we apply artificial, nonlinear deformations ($T_{ap}$) of various magnitudes and angles to each quadrant of a sectioned $T_1$ to generate an image $T_1^d$; the inverse of the applied deformation ($T_{ap}^{-1}$) is stored. This procedure is repeated 100 times to result in 100 distinct $T_1^d$ images and ultimately producing 100 known ($T_{ap}^{-1}$).

5.1.2 Registration Experiment
The goal of the registration task here is to recover synthetic deformations on images with noise using FFD with the SDM regularizer. A 100 fold leave-one-out study is conducted, whereby a SDM is repeatedly trained using 99 ($T_{ap}^{-1}$), then incorporated within FFD as a regularizer. Finally, the SDM regularized FFD is tested on the remaining deformed image with induced noise, denoted as $T_1^t$. Three different types of noise are selected for use in this experiment – Gaussian, salt and pepper and speckle (multiplicative). Overall, for $T_1^t$, six different conditions were generated: 3 types of noise and a high and low amount for each type. Both gaussian and salt and pepper were introduced with a mean of 0.04 and 0.4, for low and high conditions, and variance of 0.03. Speckle was induced with a noise density of 0.03 and 0.3 for low and high conditions. The recovered image, denoted $T_1^r$, and the corresponding corrective deformation ($T_{MT}$) induced by regularized FFD are evaluated qualitatively and quantitatively. For comparison, unregularized FFD is utilized to obtain a recovered image $T_1^{r'}$ and deformation field $T_{MT'}$.

5.1.3 Registration Evaluation
Quantitative evaluation of registration accuracy for synthetic data can be performed easily since the exact inverse deformation ($T_{ap}^{-1}$) and induced corrective deformation $T_{MT}$ and $T_{MT'}$ for regularized and unregularized FFD, respectively, are known. The magnitude of error in the transformations may be quantified by the mean absolute distance (MAD) and root mean squared (RMS) error. Both of these evaluation methods are computed over the $N$ total image pixels $c$ in the common coordinate frame $C$ of $T_1$ and can be expressed as:

$$MAD (T_{MT}) = \frac{1}{N} \sum_{c \in C} \| T_{MT}(c) - (T_{ap})^{-1}(c) \|_2,$$

$$RMS (T_{MT}) = \sqrt{\frac{1}{N} \sum_{c \in C} (T_{MT}(c) - (T_{ap})^{-1}(c))_2^2},$$

where $N = |C|$ and $\| \cdot \|_2$ represents the $L_2$ norm. Additionally, we use normalized cross correlation (NCC) as the similarity measure to directly compare the original $T_1$ and $T_1'$. We define NCC in the following manner:

$$NCC (T_1, T_1') = \left\langle \frac{T_1 - \overline{T_1}}{\| T_1 - \overline{T_1} \|_2}, \frac{T_1' - \overline{T_1'}}{\| T_1' - \overline{T_1'} \|_2} \right\rangle,$$

where $\overline{T_1}$ represents the mean intensity, $\| \cdot \|_2$ again represents the $L_2$ norm, and $\langle \cdot, \cdot \rangle$ represents the inner product.
5.2 Clinical in vivo prostate MRI and ex vivo histology

5.2.1 Data Description

We address the registration of a prostate data set $S^c$ comprising multimodal T2-w MRI and WMH images, denoted via $S$ and $H$, respectively. More specifically, $S^c$ comprises 86 ex vivo WMH sections and 4 Tesla (T) T2-w axial MRI over all 22 patient studies. Slice correspondences between MRI and histology were determined via a method previously developed and presented by Xiao et al.\textsuperscript{6} Each T2-w MRI of the prostate was acquired from patients scheduled for radical prostatectomy at the Hospital at the University of Pennsylvania using a whole body Siemens Trio MR scanner in conjunction with a 2D fast spin echo, TE 126 msec, TR 3000, 15.6 Khz, and 4 signal averages. Following removal of the prostate, ex vivo tissue specimens were preserved in a Plexiglas box containing 2% agar. A rotary knife was used to section the gland and generate 4 $\mu$m thick histological slices at 1.5 mm intervals, with each histological slice produced in this manner corresponding to every second MRI slice. All histological slices were stained with Hematoxylin and Eosin to distinguish and illuminate the nucleus, cytoskeleton and extracellular matrix of prostate cells to aid in diagnostic analysis. The slices were then sectioned into quarters to allow for digital scanning using a whole slide scanner. We employed the interactive software, Histostitcher\textsuperscript{24} to permit accurate and rapid reassembly of histology fragments into pseudo whole mount histology sections.\textsuperscript{25}

5.2.2 Registration Experiment

The goal of the registration task was to provide an accurate overlay of ex vivo pseudo WMH on the prostate of in vivo MRI slices. We exploit thin-plate splines (TPS) to manually register 80 matching $H$ and $S$ slices and use the resulting 80 deformation fields to train a SDM. The SDM regularized FFD was then utilized to register the remaining 6 $H$ sections with their corresponding $S$ slices. Prior to multimodal registration, all $H$ sections were rotated, translated and scaled isotropically to match the size and localization of prostate on corresponding $S$ slices. Further, we manually select a bounding box to initialize the transformation since various anatomical structures found on the histology may be not be visibly apparent on MRI.

5.2.3 Registration Evaluation

Quantitative evaluation of clinical data sets is difficult to perform since the exact deformation required for the correct overlay is unknown. Therefore, the extent of alignment is computed using MAD and RMS between landmarks, signifying key structures on both modalities, identified on the deformed $H$, denoted $H^d$, and the corresponding $S$ slices by expert radiologists.

5.3 Implementation Details

The SDM regularizer was implemented in MATLAB and run with FFD on a machine with 8 cores (each 2.67 GHz) and 32 GB of memory running Debian Linux. A Nelder-Mead optimization scheme, also known as the amoeba method, was used to solve Equation (1). For synthetic experiments, the regularized registration took approximately 90 seconds, with standard FFD taking 10 to 20 seconds less. Similarly, for the registration of histology and MRI, regularized FFD took 120 seconds, whereas standard FFD averaged approximately 100 seconds.

6. RESULTS AND DISCUSSION

6.1 Synthetic brain MRI

6.1.1 Quantitative Results

Figure 3 illustrates a comparison of the evaluation measures MAD and RMS for transformations obtained in the elastic registration of the testing image $T_1^r$ and original image $T_1$ using standard, unregularized FFD and SDM regularized FFD. Additionally, NCC values computed directly using these two images are also reported for both methods in Figure 3. As much as a 19% increase in NCC and a 16% decrease in RMS and MAD were observed upon inclusion of prior knowledge regarding the registration task in FFD. The values of MAD, RMS and NCC were compared between $T^{MT}$ and $T^{MT'}$ using a Student’s paired t-test under the null hypothesis that there was no difference in MAD, RMS or NCC between $T^{MT}$ and $T^{MT'}$. Table 2 presents a summary of the results
Table 2: Comparison of elastic registration accuracy for unregularized and SDM regularized FFD alignment for T1-w synthetic MRI brain images (n=100). Results from multiple paired t-tests (p-values for all tests shown below) indicate significant improvement in registration outcomes upon inclusion of the SDM regularizer in the presence of high amount of noise. Values of $p<0.05$ have been marked with a single asterisk and $p<0.01$ have been marked with a doubled asterisk.

<table>
<thead>
<tr>
<th>Type of Noise</th>
<th>Level of Noise</th>
<th>$p_{MAD}$</th>
<th>$p_{RMS}$</th>
<th>$p_{NCC}$</th>
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<tr>
<td>Gaussian</td>
<td>Low</td>
<td>0.0459*</td>
<td>0.0523</td>
<td>1.23×10^{-4}***</td>
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<tr>
<td></td>
<td>High</td>
<td>1.56×10^{-5}**</td>
<td>2.96×10^{-3}***</td>
<td>3.42×10^{-8}***</td>
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<tr>
<td>Salt &amp; Pepper</td>
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<td>0.0921</td>
<td>0.0689</td>
<td>6.21×10^{-4}***</td>
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<tr>
<td></td>
<td>High</td>
<td>0.0231*</td>
<td>0.0122*</td>
<td>9.29×10^{-7}***</td>
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<tr>
<td>Speckle</td>
<td>Low</td>
<td>0.156</td>
<td>0.0843</td>
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<td></td>
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</table>

from each t-test. Across all evaluation measures, SDM regularized FFD performs with a significantly lower error ($p<0.05$ for n=100) compared to unregularized FFD in the presence of high levels of noise. For low degrees of noise, outcomes vary, regularized FFD appears to marginally outperform unregularized FFD. For non-noisy data, because FFD already performs well, there is little room of improvement by adding the SDM.

6.1.2 Qualitative Results

Figure 4 illustrates the qualitative results of registration in the synthetic data. A superior registration subsequent to the inclusion of the SDM regularizer is clear comparing the difference images. Regions of significant discrepancies, indicated by warm colors, are more abundant in the unregularized (4(i)) than regularized (4(j)) alignment. Again, it is apparent here that a lack of prior knowledge in the registration scheme causes a poor registration result. The same can be gleaned from the reported ($T_{ap}$)\(^{-1}\) (4(f)), $T_{MT}$ (4(h)) and $T_{MT}'$ (4(g)). It is readily seen that $T_{MT}'$ drastically diverges from ($T_{ap}$)\(^{-1}\), whereas $T_{MT}$ closely resembles it. A marked improvement is observed when exploiting a SDM model trained with known deformations in the registration scheme.

6.2 Clinical prostate MRI and histology

6.2.1 Quantitative Results

Figure 5 presents a summary of the results from the clinical registration tasks. For unregularized FFD, MAD between landmarks ranged from 1.889 mm to 2.047 mm and RMS ranged from 2.010 mm to 2.891 mm. Mean value of DICE, reported separately in Table 3, across all 6 studies was 0.693, indicating a very poor alignment of the prostate between MRI and histology. On the other hand, for SDM regularized FFD, MAD oscillated between 0.623 mm and 1.297 mm and RMS oscillated between 1.015 mm and 1.753 mm. The mean DICE value of 0.845 suggests a high degree of prostate alignment between the two modalities. The quantitative results suggest that by modulating the registration of WMH and MRI, the SDM regularizer is able to achieve better registration performance.

6.2.2 Qualitative Results

As evident from Figure 6, when driven solely by intensity-based information, FFD induces incorrect deformations on $H$ slices (6(a) and 6(e)) and produces $H^d$ images that are in mis-alignment with $S$ (6(b) and 6(f)). The unregularized registration scheme (6(c) and 6(g)) fails to recognize that the prostate only spans the center of $S$ and simply searches for transformations that optimize the similarity measure without being aware of which transformations might be valid. Therefore, the landmarks, shown in red for MRI and yellow for histology, are in different positions. Observing the overlay images (6(d) and 6(h)) produced from utilizing the proposed regularizer, an accurate alignment is seen in which $H^d$ is contained within the prostate capsule found in the center of $S$. Unlike the unregularized case, here, the landmarks overlap properly after the registration.
Figure 3: Quantitative comparison of unregularized and regularized FFD using MAD, RMS and NCC. Decrease in RMS and MAD and a similar increase in NCC is discernible using the SDM in the presence of high levels of noise. For low levels of noise, the SDM regularizer has a negligible effect in the registration. Two asterisks reflect \( p<0.01 \) very high statistical significance and a single asterisk \( p<0.05 \) indicates statistical significance.

Figure 4: Qualitative comparison of unregularized FFD and SDM regularized FFD registration of images with a high degree of noise. (a) The \( T_1 \), (b) \( T_1^d \) image, corresponding (c) \( T_1^d \) and the resulting registration outcomes (d) \( T_1^r \) and (e) \( T_1^r \) are all shown. Deformation fields (f) \((T^{op})^{-1}\), (g) \(T^{MT}\) and (h) \(T^{MT}\) are also displayed. A marked improvement in registration is apparent from comparison of the difference images arising from un-regularized and regularized FFD, (i) and (h), respectively. Larger errors are assigned warmer colors and lower errors are assigned cooler colors.
Figure 5: Comparison of elastic registration accuracy for unregularized and SDM regularized FFD alignment of 6 histological and corresponding MRI images from 2 patients. As before, MAD and RMS between landmarks are given in millimeters. Mean values for evaluation measures are shown. Note that the SDM regularizer yields improved results over FFD alone across all 6 slices.

Figure 6: Two studies for which the histostitched pseudo WMH sections are registered to corresponding in vivo endorectal T2-w MRI. (a)-(d) and (e)-(h) represent studies 1 and 2. (a) and (e) are the the digitized WMH slices subject to deformation. (b) and (f) are fixed in vivo MRI. (c) and (g) are magnified regions of interest obtained from unregularized FFD. Finally, (d) and (h) illustrate the improvement from incorporation of a SDM regularizer. Prostate segmentations are shown in blue on all MRI images to assess quality of registration. Further, positions of landmarks, indicated in red for MRI and yellow for histology, are shown in each image.
Table 3: Evaluation of the multimodal registration of histology and MRI using DICE. In all six cases, SDM regularizer improves the quality of the registration.

<table>
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<th>Slice</th>
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7. CONCLUDING REMARKS AND FUTURE DIRECTION

In this paper, we have developed and presented a novel application of the SDM regularizer for multimodal image registration of pseudo whole mount histology to T2-w MRI of the prostate gland. The SDM is trained using a known set of deformation fields derived from the repeated manual registration of appropriate images using thin-plate splines. Subsequent inclusion within the FFD registration formulation as a regularizer allows for the computation of likelihood values for all potential transformations. The likelihood values, low when deformations differ greatly from the training set and high when very similar, are scaled and used to influence the similarity measure to either constrain or allow a transformation. In addition to improved outcomes, this regularizer empowers FFD to proceed smoothly in the presence of any type of artifacts (noise, bias-field etc.) found in images.

Our scheme for registration of in vivo MRI and ex vivo psuedo whole mount histology is distinct from previous approaches in that (1) information from a SDM is leveraged to drive the process of automated non-rigid registration with histology; (2) no additional, intermediate ex vivo radiology or gross histology images need to be obtained in addition to the clinically acquired in vivo MRI series; and (3) no point correspondences are required to be identified manually or automatically. Our scheme also does not require explicit segmentation of the prostate on MRI prior to registration with WMH. If the spatial extent of prostate cancer on in vivo radiological imaging can be accurately delineated, it may then be possible to develop specific imaging parameters that reliably characterize prostate cancer on in vivo clinical, radiologic images. These signatures for diseases may be used to develop accurate computer-assisted detection systems for cancer and assist in the training of medical students, radiology residents, and fellows.

8. ACKNOWLEDGMENTS

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